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14. ABSTRACT

This program is intended to establish the infrastructure to provide state-of-the art targeted radiation therapy to military personnel and veterans with cancer. The research aspect of this project is intended to demonstrate whether 1) targeted radiation therapy with real time localization and tracking will allow use of a smaller planning treatment volume margin with a significant decrease in rectal and bladder volume treated and whether the use of such targeted therapy can occur within standard treatment times and thus feasible for routine clinical use, 2) whether the use of Vac-Lok® immobilization devices are necessary when patients are treated using the Calypso system, 3) whether Beacon® Transponder is of benefit in pelvic radiation therapy following prostatectomy, 4) whether hypofractionated treatment plans which are more beam on time per fraction which may potentially account for more intra-fraction organ movement but allow for a shorter duration of treatment are feasible for routine clinical use with the Calypso system and 5) whether use of the Calypso system, and other advanced radiation therapy equipment, can improve treatment techniques and outcomes in malignancies arising in other parts of the body.

15. SUBJECT TERMS
Calypso, Prostate, Intensity Modulated Radiation Therapy (IMRT), Planning Target Volume (PTV), Beacon Transponders

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Targeted Radiation Therapy for Cancer Initiative Annual Report

Introduction:

The full potential of radiation therapy has not been realized due to the inability to locate and track the tumor target continuously during the delivery of the radiation dose. Without the ability to accurately locate the tumor target at the time of dose delivery, more of the patient's healthy tissue is exposed to radiation, which may result in acute or chronic complications. The research studies and activities described will improve the techniques of modern radiation therapy and directly benefit the Departments of Defense and Veterans Affairs by: providing improved, state-of-the-art prostate cancer treatments to active-duty military personnel and veterans; continuing to investigate reduction of the number of daily radiation treatments required for each patient thereby reducing the cost of care and increasing treatment capacity within the military delivery system; enabling research to establish standards of care for targeted radiation therapy; establishing a DOD center of excellence in targeted radiation therapy and accelerating the development of the targeted radiation therapy platform to treat additional cancers that significantly affect service personnel, their families, and veterans, such as breast cancer and metastatic cancer. The Calypso® 4D Localization System is utilized to track both inter-fraction and intra-fraction tumor movement in patients receiving radiation therapy for various malignancies. Improved tracking of tumors may lead to improved therapeutic outcomes. The Calypso® 4D Localization System is a FDA Class II device.

Body: Task Completion

Task 1. *Establishment of centers for targeted radiation therapy at MAMC and VAPSHCS with installation of the Calypso® 4D Localization System.*

Installation of the Calypso® 4D Localization System occurred at MAMC. The radiation team continues to receive training and technical support of the system from Calypso as needed.

The installation and training of the Calypso System also occurred at VAPSHCS. However, the system is not being used and will be de-installed soon and re-installed at MAMC to be used with our forthcoming treatment machine. This is further explained in section III of this report.

Task 2. *Treatment for prostate cancer with state-of-the art technology to allow real-time localization and continuous tracking of the tumor target.*

A total of 19 non-study prostate cancer patients who did not otherwise qualify for a protocol have been treated with the Calypso system at MAMC. Non-protocol patients have allowed the providers to gain further proficiency with the Calypso unit. Four of these patients have been treated in the prone position. The experience and knowledge gained in this alternative positioning technique has allowed for patients who were not anatomically compatible with the Calypso system in the supine position to be able to receive treatment with this state-of-the-art localizing/tracking device. The Reduced Margins protocol was amended to allow for prone positioning and we anticipate amending the Immobilization (high-risk stratification sub-set) also.

MAMC has also recently used the newly approved FDA surface transponders off protocol to monitor breathing motion during our standard breath-hold technique for treating left-sided breast cancer, which allows sparing of the heart. The Calypso system provides a previously unavailable level of additional positional monitoring for these patients and we have gained considerable expertise with this technique. We expect to open a breast cancer protocol in the near future which will prospectively evaluate the benefits of this technique, including quantifying dose reduction to the heart.

VAPSHCS completed treatment on one non-protocol patient.

Task 3. *Feasibility study with reduced planning treatment volume (PTV) margins and intensity modulated radiation therapy (IMRT) using targeted radiation therapy.*

Fourteen subjects have been consented and enrolled in the study with Reduced PTV Margins at MAMC to date. Eight of these subjects have completed the trial and six are in the follow-up phase.

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1. Pt. #1009 was out of window for his month 12 follow-up visit by 9 days from the allowed +/- 2 week window due to being out of town. 2. Continuing review was approved by the MAMC IRB and HRPO from 19 July 2012 through 18 July 2013. All potential patients that are seen at the weekly multidisciplinary prostate cancer clinic and or by provider referral are being considered for participation and are given the option to partake.

VAPSHCS received full regulatory approval, but never consented any subjects. This site is now closed.

In an effort to boost enrollment, we have collaborated with Brooke Army Medical Center. BAMC is currently treating patients using the Calypso system (non-protocol patients not under this grant) and has an abundant subject population that meet the protocol requirements. Now that we have received sponsor approval to add this site, we are in the process of getting BAMC regulatory approval for this protocol. The amendment package has been submitted for MAMC IRB review.

By joining forces with BAMC, we feel optimistic that we will meet our accrual goals.

This study is expected to enroll a combined total of 20 subjects from both centers.

Task 4. *A Hypofractionated IMRT Therapy in Patients with Favorable Risk Prostate Cancer Using the Calypso® 4D Localization System: A Feasibility Study.*

We are currently pursing participation in the open RTOG 0938 study, which randomizes patients between a 12 fraction treatment and a 5 fraction treatment. We have successfully credentialed our VMAT and IMRT delivery processes through the RTOG, and are awaiting approval on our IGRT technique. To our knowledge we will be one of the first sites, if not the first site to use Calypso localization on this study. Participation in RTOG 0938 will allow us to help answer an important research question being addressed at the national level, and we will be able to contribute our expertise with Calypso localization in this setting. Our participation will also contribute significantly towards the overarching goal of establishing a center of excellence for targeted prostate cancer radiation therapy. We expect to receive approval from RTOG sponsor to participate in this trial soon. We will then submit a revised statement of work to MRMC for review and approval before submitting for MAMC regulatory approval.

This study is expected to enroll 20 subjects.

Task 5. *A Randomized Study Comparing External Pelvic Immobilization to Limited Immobilization for the Treatment of Prostate Cancer with IMRT Using Real-Time, State -of-the-Art Motion Tracking with the Calypso® 4D Localization System.*

Eight subjects have been enrolled in the Immobilization study at MAMC to date. A total of eleven signed consent; three were screen failures and never started treatment. Four of these subjects have completed the study and four are in the follow-up phase.

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1. The Protocol and ICF were amended to no longer randomize the subset of high-risk patients. In this protocol, we were randomizing patients to limited immobilization vs. vac-loc immobilization. Over the past two (2) years since the protocol's inception, radiation therapy techniques have continued to evolve. In the subset of high-risk patients, research continues as to how improved prostate immobilization affects decisions about margins for the lymph node target. In this newly evolved setting, it is unlikely that clinicians would consider treating high risk patients without an immobilization device, even with Calypso tracking. We therefore decided to adapt our randomized study to the changing treatment climate by no longer randomizing the subset of high-risk patients to possibly receive treatment without an immobilization device. All high-risk patients will receive treatment with Calypso tracking and a vac-loc immobilization device, and we will increase the robustness of our data collection in these patients to allow evaluation of lymph node positioning relative to Calypso positioning at the conclusion of the study. 2. The continuing review is scheduled to occur on 28 August 2012. The current review approval period is from 30 August 2011 through 29 August 2012.

VAPSHCS received partial regulatory approval. No subjects were ever consented. This site is now closed.

This study is expected to enroll a combined total of 20 subjects from both centers.

Task 6. *Post-prostatectomy Daily Target Guided Radiotherapy Using Real-Time, State-of-the-Art Motion Tracking with the Calypso® 4D Localization System: A Feasibility Study.*

Ten subjects have been enrolled in the Immobilization study at MAMC to date. A total of fourteen have signed consent; three were screen failures and never started treatment and one is scheduled to start treatment in September. Four of these subjects have completed the study and seven are in the follow-up phase.

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1. Enrollment was increased from 10 to 20 subjects. In order to request this change we performed an initial review of the data collected on this protocol to date. Initial quantitative review of the Calypso data for the first nine subjects demonstrates average shifts from initial set-up of 0.20 cm (lateral – positive to the right), 1.08 cm (longitudinal), and 0.14 cm (vertical). These measurements are within the expected range, although in reality they are more a check of standard set-up procedures than of actual target localization and do not have bearing on the treated target. Average distance between transponders were: apex to left base -0.07 cm, right base to left base -0.06 cm, apex to right base -0.08 cm. Average maximum excursion for all fractions was 0.06 cm to the left, 0.06 cm to the right, 0.12 cm to the superior, 0.12 cm to the inferior, 0.02 cm to the anterior, 0.25 cm to the posterior. These values fall well within our planning target volume (PTV) limits of 1 cm circumferentially with the option to reduce posterior expansion to 0.6 cm. Qualitative (daily, during each patient's treatment course) analysis of daily cone-beam CT scans demonstrates target volumes to cover specified targets in all cases.
2. The current review approval period is from 24 April 2012 through 24 October 2012.

Our quantitative analysis of the cone-beam CT scan data is currently underway, and we expect submission for publication this fall. The data gathered from this process will enable us to determine how much we can safely reduce the PTV margins for a follow-on reduced PTV margins study. This data also provides an unprecedented and detailed description of inter- and intra- fraction changes in prostate bed morphology and targeting, which will also be useful for clinics using localization strategies other than Calypso. The localization data captured from this protocol and from any future follow-on reduced PTV margins protocol will eventually

be analyzed in aggregate to provide an extraordinarily robust database on localizing the prostatic fossa using Calypso beacons.

VAPSHCS received partial regulatory approval. No subjects were ever consented. This site is now closed.

This study is expected to enroll 20 subjects.

Task 7. *Phase I/II trial of Real Time targeting of metastatic lesions in the liver with hypofractionated radiation therapy.*

Based on review of the current patient population, it has been determined that it would be unlikely that we would be able to enroll enough subjects for any statistical value. In addition to, the Calypso System is not FDA approved at this time for this indication.

We do plan on initiating another protocol in lieu of this one. Our plan is to open a Reduced Margins Post-Prostatectomy study based on our data analysis of the ongoing Post-Prostatectomy trial as mentioned in task # 6.

We are also currently working on a breathing motion in breast cancer trial (which would not affect patient treatment). In this trial we would use Calypso beacons placed on the skin surface to track breathing motion during a breath-hold technique for left-sided breast cancer treatment. Analysis would reveal the potential for using such a set-up to gate left-sided breast cancer treatments to reduce dose to the heart, or for the purposes of external beam accelerated partial breast irradiation, a technique currently being evaluated in a randomized national study. We have been exploring the logistics and background work on this idea and in fact have used this technique as an adjunct to our standard technique in 7 (non-protocol) patients with great success.

We are also in the development phase of a multi-disciplinary randomized study of central dose escalation in our palliative patients. Recent technical advances allow treatment of the center of metastatic lesions to significantly increased dose, without increasing the dose to normal surrounding tissues. Despite this, in general radiation oncologists do not use this technology for palliative patients, but treat as we have historically, providing a modest uniform dose to the region of the body in question. In our proposed randomized trial, we will compare standard dose palliative radiation therapy with palliative radiation which maintains standard normal tissue doses while “boosting” the center of the metastatic lesion to a dose 20 – 40% higher. Our hypothesis is that this will combat the common central hypo-oxygenation found in tumors and lead to an improved and protracted treatment response. Standard normal tissue doses and safety margins will be respected throughout, making our experimental arm equivalently safe in comparison to our standard arm. Outcome measures will include toxicity, radiographic response, and palliative response. Recent research also suggests the possibility that focal, high radiation doses to tumor regions bring about an anti-tumor immunologic response. Therefore, as part of this study we would also like to develop a biorepository of tissue or blood samples to evaluate any immunologic changes incurred as a result of this treatment.

Since the scope of Task 7 will be significantly revised, a new Statement of Work will be completed and sent to MRMC for review and approval.

The team looks forward to discussing with MRMC the above ideas as well as the target areas of research that CDMRP is interested in pursuing.

Task 8. *Establish a center of excellence for targeted radiation therapy.*

The staff at MAMC have treated approximately 60 patients with the Calypso® 4D Localization System and continue to develop expertise as a center of excellence in targeted radiation therapy. This grant continues to facilitate continuing medical education for the staff at MAMC on image guided radiotherapy. Additional education materials and visits from other DOD providers will be coordinated in upcoming years of the project.

An active duty Army Radiation Oncologist resident is scheduled to rotate at MAMC in beginning on 30 August 2012. The resident will learn advanced techniques of tumor targeting with the Calypso system and be given the opportunity to evaluate data and take part in writing scientific papers under the guidance of the MAMC physicians.

We have hosted three educational conferences/visiting professorships in the area of urology and radiation oncology thus far. Our last speaker was Shiv Srivastava, Ph.D., an established cancer researcher in a leadership position with a strong academic/administrative track record in the cancer biology and translational research. Approximately 30 attendees attended his lecture, "ERG, a Common Oncogenic Activation in Prostate Cancer From Discovery to Translation". With the continued success of these symposiums, we have committed to making these events an annual occurrence. We believe these educational events promote our site as a "center of excellence in target radiation therapy" and encourage physicians in the community to seek our expertise.

We continue to collect information regarding problems/challenges encountered with Calypso as a "Lessons Learned Log" which identifies the problems encountered with possible causes and the techniques used to solve the problem.

Task 9: *Present findings of feasibility studies at professional conference.*

We presented a poster presentation based on the initial findings of the Reduced PTV margins feasibility study at the ASCO/ASTRO/SUO Genitourinary Oncology Symposium in February 2012. Two of the authors attended the conference and presented the poster. We received positive remarks and feedback on this early study which demonstrated the potential impact of reducing PTV margins and also described a detailed method for tracking dose to the muscles of the pelvic floor.

Problem Areas:

As previously reported, it was unanimously decided to discontinue efforts at VAPSHCS based on several factors which included: radiation therapy staffing issues at the VA, the slow pace of the VA IRB system, and most fundamentally the practice pattern of the Seattle VA which focuses on brachytherapy as treatment for prostate cancer. It seemed unlikely that patient accrual would substantially contribute to our research.

The Calypso System at the VA will be de-installed and moved MAMC to be used with our forthcoming treatment machine. We will have the capability to perform stereotactic treatments, and will be able to have more accurate collimation. Having a Calypso device in the vault with the new machine will allow us to incorporate the benefits of the new machine for our Calypso patients. For example, we could consider using the Calypso device for stereotactic treatments (on protocol, once we designed such a protocol), and could also have even better control of our radiation for prostate cancer treatments (because of the finer collimator).

There has been a delay in getting Brooke Army Medical Center added as an additional site on this grant to support the Reduced PTV margins protocol. The physician originally identified to be the site PI, MAJ Dullea, was deployed. BAMC has identified MAJ Stall, another radiation oncologist at the site to fulfill this role until MAJ Dullea returns. We are currently working on the regulatory aspects of adding

this site. The regulatory packet was submitted for MAMC IRB review and put on the meeting agenda for 28 August 2012.

Key Personnel Updates:

Investigators from VAPSHCS were removed from the protocol.

Key Research Accomplishments:

- Enrolled/Consented 14 subjects on the Reduced PTV Margins protocol
- Enrolled 8 subjects (consented 11) on the Immobilization protocol
- Enrolled 10 (consented 14) subjects on the Post-prostatectomy protocol
- Treated 27 non-study patients with Calypso (including prostate and breast).
- Developed a database of volumetric and dosimetric anatomical data correlated with patient quality of life outcomes for patients treated on the reduced PTV margins study.
- Developed a database of anatomical data describing quantitatively the morphology of the prostatic fossa measured on over 300 treatment-matched CT scans in post-prostatectomy patients receiving radiation therapy.
- Continued development of Madigan as a center of excellence in Targeted Radiation therapy, including continued success of our annual multidisciplinary educational conference/visiting professorship.
- Developed technical expertise in using Calypso surface beacons to track breathing motion in left-sided breast cancer, allowing sparing of the heart.

Reportable Outcomes:

Abstract title: "Dose to the Muscles of Fecal Continence During Radiation Therapy for Prostate Cancer Using Calypso Localization." Poster was presented at the ASCO/ASTRO/SUO Genitourinary Oncology Symposium in February 2012.

Submitted an Abstract to the 2013 ASTRO/RSNA Cancer Imaging and Radiation Oncology Symposium titled, "Anorectal Angle is Associated With Bowel Toxicity One Month Following Radiation Therapy for Prostate Cancer." We are awaiting word regarding acceptance of this abstract.

Two research assistants have been provided employment supported by this research grant. Their work on this project has been fundamental in collecting data for our current and future research.

Conclusion: The "Targeted Radiation Therapy for Cancer Initiative" has provided a framework for developing Madigan Radiation Oncology into a center of excellence for targeted radiation therapy. Now we see our research momentum increasing, particularly as our prospective studies begin to mature.

Our currently underway analysis of our new database of post-prostatectomy anatomical information in over 300 treatment fractions will allow an unprecedented look at the inter- and intra- fraction changes in morphology of the prostatic fossa. Our planned participation in RTOG 0938 will allow us to contribute our expertise with Calypso localization to the national research question regarding extreme hypofractionation in prostate cancer.

The continued accrual to our reduced PTV margins protocol, and participation of BAMC in this protocol, will lead to important quality of life outcomes publications in prostate cancer.

The research and education opportunities afforded by this progress has not gone unnoticed. On our most recent abstract submission we have active collaboration with the Madigan Radiology Department; a collaboration which we hope will expand. We also were able to include members of the pathology department in our visiting professorship this year, and hope to develop research collaboration with the pathology department in the upcoming year.

As discussed in this report, we are moving toward exciting new areas of research, including use of Calypso beacons to track breathing motion in breast cancer patients and using targeted radiation therapy modalities to improve our decades-old methods for treating metastatic lesions in the palliative setting. In addition to these areas of investigation we also envision in the distant future developing expertise with Calypso beacons implanted in the lung and other sites.

We are working hard to conserve our grant money (including redistributing our budget to cover a requested one or two-year no-cost extension), but foresee the inevitable exhaustion of our funds long before completion of our envisioned breast and palliative protocols. To this end, we are planning in upcoming months to request further funding from MRMC.

This is an exciting era for targeted radiation therapy. With the help of the Congressionally Directed Medical Research Program we plan to treat our patients – military servicemen and women and their families – with lifesaving technology at the forefront of our field for years to come.

References: N/A

Appendices: See attached abstract

APPENDIX

Abstract: Dose to the muscles of fecal continence during radiation therapy for prostate cancer.

INTRODUCTION AND OBJECTIVE: Radiation therapy for prostate cancer can lead to loss of fecal continence; our understanding of the dose-volume relationships of this late toxicity continues to develop. The external anal sphincter (EAS), internal anal sphincter (IAS), the puborectalis (PRM), the pubococcygeus (PCM), and the illiococcygeus (ICM) muscles all contribute to fecal continence. We developed a reproducible method for contouring these muscles and in this preliminary study evaluate whether decreased planning target volume (PTV) margins lead to potentially clinically significant decreases in dose to these muscles during definitive radiation therapy for prostate cancer.

METHODS: Muscles involved in fecal continence were contoured for 10 consecutive patients on a prospective study of reduced PTV margins for treating low-to-intermediate risk prostate cancer with intensity modulated radiation therapy (IMRT) using an electromagnetic localization system. IMRT plans to a prescribed dose of 7740 cGy were developed using 10mm PTV margins (5mm posteriorly), and compared with actual treatment IMRT plans using 3mm circumferential PTV margins. Decreases in dose were evaluated for statistical significance using an unpaired t-test.

RESULTS: Reducing PTV margins decreased the mean PTV volume from 176.2 ml to 91.9 ml. Mean doses to the EAS, IAS, and rectum (REC) decreased significantly; from 11.0 Gy to 4.1 Gy ($p=0.005$), from 30.5 Gy to 15.0 Gy ($p = 0.004$), and from 43.7 Gy to 35.6 Gy ($p=0.006$) respectively. Decrease in the mean dose to the PRM was nearly statistically significant, 48.7 Gy to 34.6 Gy ($p = 0.055$). Decreases in mean doses to the PCM and ICM were not statistically significant; from 61.9 Gy to 55.2 Gy ($p = 0.107$), and from 40.7 Gy to 34.8 Gy ($p = 0.176$), respectively.

CONCLUSIONS: Using electromagnetic tracking to reduce PTV margins leads to a significant decrease in dose to the muscles of fecal continence, with mean dose decreases in a range that may be clinically significant.